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09/744,103	12/10/2001	Anthony Boey	20801-000810	3038

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TOWNSEND AND TOWNSEND AND CREW, LLP
TWO EMBARCADERO CENTER
EIGHTH FLOOR
SAN FRANCISCO, CA 94111-3834

EXAMINER	
KISHORE, GOLLAMUDI S	
ART UNIT	PAPER NUMBER
1612	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/744,103	BOEY ET AL.	
	Examiner	Art Unit	
	Gollamudi S. Kishore, Ph.D	1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 February 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11,14-29,31-54 and 67-72* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11,14-29,31-54 and 67-72* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The RCE dated 2-4-09 is acknowledged.

Claims included in the prosecution are 1-11, 14-29, 31-54 and 67-72.

In view of the amendments, the 102 rejections are withdrawn.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims -11, 14-29, 31-54 and 67-72 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant amends claim 1 to introduce the limitation, 'wherein at least about 30 % of said condensing agent-nucleic acid complexes -----". This limitation implies the upper limit can be even 100 %. A careful review of the specification however, indicates that the upper limit is 70 % (see page 19, lines 15-18). Similarly, the sizes recited on page 18 of the specification are from 20 to 200 nm, more preferably from 50 to 150 nm and especially in preferred embodiment, they are 70 nm to 80 nm. The newly introduced limitation is "less than about 100 nm. Therefore, the introduced limitations are deemed to be new matter since there is no support in the specification originally filed for these limitations.

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 3, 15-25 and 43-49 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

It is unclear as to what applicant intends to convey by 'reversibly associated' in claim 3. The bilayer stabilizing agents according to the dependent claim 15 include lipids and therefore would sequester in the bilayers just like phospholipids making up the liposomes. Does the term imply even the phospholipids are reversibly associated? How are the lipids recited in the dependent claims (15 and 43) different from the lipid recited in the independent claims? The meets and bounds of 'lipid derivatives' in these claims are also unclear. What is the distinction between polyamide oligomer and a peptide?

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made

to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 1-11, 14-29, 31-54 and 67-72 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lee (5,908,777) or Lee (J. Biol. Chem) cited before.

Lee (777) discloses compositions containing condensed nucleic acid preparations encapsulated within the liposomes for transfection. The liposomes contain DOPE/PS and PEG-PE. The condensing agent is polylysine, protamine or spermine or spermidine. (Abstract, col. 5, line 23 through col. 7, line 64 and examples, Example 1 in particular). The sizes of the liposomes as observed in Fig.3 ranges from 100-200 nm. Although Lee does not specifically state the molecular weight of PEG, PEG-lipid complex in Lee is prepared according to the method of by Lee's previous work wherein PEG 2000 was used.

The examiner has already cited Lee BBA 1995 of interest in this context (note materials section).

Lee (J Biol. Chem) discloses compositions containing condensed nucleic acid preparations encapsulated within the liposomes for transfection. The liposomes contain DOPE/PS and PEG-PE. The condensing agent is polylysine, (abstract and the whole publication). As stated above, although Lee does not specifically state the molecular weight of PEG, PEG-lipid complex in Lee is prepared according to the method of by Lee's previous work wherein PEG 2000 was used.

Lee references lack the teachings of the percent encapsulation of the complexes. However, since the amount encapsulated depends on the molecular weights of the

nucleic acids and the condensing agents, in the absence of showing the criticality, the amounts of deemed to be manipulatable parameters. What is also lacking in Lee is the teaching of the diameters of the complex (condensing agent and the nucleic acid). Since this parameter depends upon the amount of the nucleic acid to be encapsulated, in the absence of showing of unexpected results, it is deemed obvious to one of ordinary skill in the art to manipulate the teachings of Lee with the expectation of obtaining the best possible results. Similarly, instant liposome sizes are deemed to be obvious in view of Lee's teachings on col. 8, line 54 et seq., which the size of the DNA containing liposomes depends on the charge between the complex and the anionic liposomes. Lee also lacks the teachings of the claimed lipid: nucleic acid ratios. This parameter once again is deemed to obvious to one of ordinary skill in the art in view of the relationship between the charge of the complex, the sizes of the liposomes and also because of the nature of the transfection to be carried out. Lee does not teach the addition of the condensing agent in stages or the addition of two condensing agents. However, since the purpose of the condensing agent is to condense the nucleic acid molecule and to protect the nucleic acid from degradation, in the absence of showing unexpected results, such a manipulation is deemed to be within the skill of the art.

7. Claims 1-11, 14-29, 31-54 and 67-72 are rejected under 35 U.S.C. 103(a) as being unpatentable over Martin (5,891,468).

Martin discloses compositions containing condensed nucleic acid preparations encapsulated within the liposomes for transfection. The liposomes contain PE, lipid

derivatized with PEG (1-20 mole percent). The sizes of the liposomes range from 100-150 nm (col. 7, lines 14-27, col. 8, lines 18-37, col. 16, line 14 through 65, col. 21, lines 4-21, Examples 9 and 11). Martin lacks the teachings of the percent encapsulation of the complexes. However, since the amount encapsulated depends on the molecular weights of the nucleic acids and the condensing agents, in the absence of showing the criticality, the amounts of deemed to be manipulatable parameters. Furthermore, since the method of encapsulation used by Martin is similar to instant method, it would have been obvious to one of ordinary skill in the art that similar encapsulation is to be expected.

8. Claims 7, 38, 68, 69, 71 and 72 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lee (5,908,777) or Lee (J. Biol. Chem) cited above, further in view of Wolff (5,744,335).

The teachings of Lee, 777 and J Biol. Chem have been discussed above. What is lacking in Lee is the teaching of the use of dioleoyl phosphatidylserine as the specific phosphatidylserine.

Wolff while disclosing a method of transfecting cells with liposomal complexes containing nucleic acid and DNA binding protein teaches the use of dioleoylphosphatidylethanolamine and dioleoyl phosphatidylserine for the formation of liposomes (abstract and col. 25, lines 43-55).

The use of dioleoylphosphatidylethanolamine and dioleoyl phosphatidylserine in the compositions of Lee, 777 and J. Biol. Chem, with a reasonable expectation of

success would have been obvious to one of ordinary skill in the art since Wolff teaches that this combination could be used in liposomes for the transfection of nucleic acids.

9. Claims 16-22, 28-29, 44-49 and 53-54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lee 5,908,777 or Lee, J. Bio. Chem., or Martin (5,891,468) cited above, further in view of Holland (5,885,613).

The teachings of Lee and Martin have been discussed above. What is lacking in these references are the teaching of PEG ceramide as the bilayer-stabilizing component. What are also lacking in these references are the explicit teachings of the molecular weights of PEG and PEG-lipid amounts in molar percentages.

Holland while disclosing liposomal compositions for the delivery of nucleic acids teaches that PEG when attached to phosphatidylethanolamine (PE) or ceramide (C 14-C20 ceramides) stabilizes the bilayer. The Molecular weight range of PEG is 200-10,000 and the amount of the PEG-lipid is in the range of 0.05 to 30 mole percent (abstract, col. 8, line 60 through col. 9, line 57, col. 24, line 4 through col. 25, line 46 and claims).

The use of PEG-ceramide as the PEG lipid instead of PEG-PE would have been obvious to one of ordinary skill in the art since Holland teaches the effectiveness of both PEG-PE and PEG-ceramide in liposome compositions used in the delivery of nucleic acids. Choosing the appropriate amounts of PEG-lipid and PEG with desired molecular weight with a reasonable expectation of success would have been obvious to one of ordinary skill in the art since Holland teaches manipulations with these parameters.

10. Claims 8-10, 23-25, 39-40, 50-51 and 71-72 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lee (5,908,777), or Lee (J. Biol. Chem), or Martin (5,891,468) cited above, further in view of Lisziewicz (6,420,176).

The teachings of Lee or Martin have been discussed above. What are lacking in these references are the teachings of the use of polyethylenimine as the polycation or the condensing agent.

Lisziewicz while disclosing compositions for delivering DNA into cells teaches that the cationic polymer, polyethylenimine (PEI 25 kD) is effective in binding to DNA and makes a complex and this complex can enter into endosomes of the skin's antigen presenting cells, Langerhans cells, via asialoglycoprotein receptor-mediated endocytosis (abstract, col. 10, line 24 et seq., and claims).

The use of PEI as the polycation in the teachings of Lee or Martin with a reasonable expectation of success since Lisziewicz teaches the ability of this polycation to bind to DNA and effectively enter into endosomes of the skin's antigen presenting cells, Langerhans cells, via asialoglycoprotein receptor-mediated endocytosis.

Applicant's arguments have been fully considered, but are moot in view of the new rejections.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gollamudi S. Kishore, Ph.D whose telephone number is (571) 272-0598. The examiner can normally be reached on 6:30 AM- 4 PM, alternate Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Krass Frederick can be reached on (571) 272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Gollamudi S Kishore/
Primary Examiner, Art Unit 1612

GSK